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Human Growth Hormone Treatment in Prepubertal Children With Achondroplasia

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We studied the effects of recombinant human growth hormone (GH) treatment in 6 prepubertal children with achondroplasia. The patients' age ranged from 2 11/12 to 8 5/12 years and the GH dose was of 0.1 IU/kg/day subcutaneously. Auxological assessments and bone age determinations were performed 6 months before, at the beginning, and after 6 and 12 months of therapy. The growth velocity increase during the whole year of treatment ranged from 1.1 to 2.6 cm/year in 3 patients while in the others no variation was detected. No side effects were observed during the trial apart from a slight advancement of bone age in two patients. MRI at the cervicomedullary junction and CT scan of the base of the skull did not show any variation of the dimensions of the foramen magnum at the end of the trial compared to baseline. Our study shows that r-hGH can safely increase short-term growth velocity in some but not all prepubertal children with achondroplasia. Our data confirm the individual variability in the response to the GH treatment. © 1996 Wiley-Liss, Inc.

KEY WORDS: achondroplasia, growth hormone, growth velocity

INTRODUCTION

Achondroplasia is one of the most common forms of osteochondrodysplasia and it is characterized by short-limbed dwarfism. Its pathogenesis is thought to involve defective endochondral ossification while periosteal and membranous ossification are normal [Rimoin et al., 1970]. It is inherited as an autosomal dominant trait, but the majority of the cases (80–90%) are sporadic. The frequency of the disorder is estimated to be around 1 in 26,000 live births [Oberklaid et al., 1979]. In the past, treatments with nonspecific drugs were performed to improve the final adult height of achondroplastic children, with negative results [Kelley and Ruvalcaba, 1982].

Growth hormone (GH) has long been known as an important regulator of linear skeletal growth. It promotes directly or indirectly, through insulin-like growth factor-1 (IGF-1), chondrocyte proliferation. The unlimited quantities of recombinant human GH (r-hGH) not only allowed treatment of GH-deficient patients, but also treatment of patients with other forms of short stature such as Turner syndrome, familial short stature [Hindmarsh et al., 1991], and hypochondroplasia [Appan et al., 1990; Bridges et al., 1991; Allen et al., 1994]. A beneficial effect of r-hGH in children with Turner syndrome has been reported by Rosenfeld et al. [1988]. Other groups have confirmed these observations [Rongen-Westerlaken et al., 1988; Vanderscheuren-Lodeweycx et al., 1990]. Recently treatment with biosynthetic hGH has been extended to achondroplasia [Okabe et al., 1991; Horton et al., 1992; Nishi et al., 1993; Yamate et al., 1993]. The trials carried out until now have shown variable responses to the treatment. The limited number of patients and the variability in the pubertal stage of the enrolled subjects make it very difficult to draw any final conclusions on the role of GH therapy in these disorders.

The purpose of our study was to evaluate the effect of the therapy with r-hGH in prepubertal achondroplastic children over a 1-year period. Another aspect of this therapeutical trial was the evaluation of its safety, with particular regard to possible negative effects on the endochondral ossification of the cranial base and upper cervical spine. In fact in achondroplasia the portions of the cranium derived from cartilage are shortened in all dimensions. As a consequence the foramen magnum is constricted and theoretically a worsening of the stenosis by GH treatment might cause brainstem compression leading to neurological and respiratory complications [Stokes et al., 1983].

SUBJECTS AND METHODS

We studied 6 children with achondroplasia, diagnosed by radiological and clinical criteria. The study

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was performed according to the Declaration of Helsinki of 1975, as revised in 1983. Informed consent was obtained from all the parents or legal guardians of the patients. The patients' age ranged from 2 11/12 to 8 5/12 years (Table I).

Exclusion criteria were the following: bone age greater than 9 years or less than 3 years, clinical signs of pubertal development, malabsorption, chronic renal or cardiac diseases, respiratory diseases, or prolonged sleep apneas.

Recombinant human GH was given subcutaneously at the dose of 0.1 IU/kg/day (18–25 IU/m^2/week).

Stature, recumbent length, weight, head circumference, sitting height, and total hand length were measured 6 months before, at the beginning, and after 6 and 12 months of therapy. Auxological assessments were performed by the same two examiners in order to reduce the error of measurements.

At the beginning and after 1 year of therapy an oral glucose tolerance test and a GH provocative test with clonidine were performed.

Thyroid function was monitored through free thyroxine (FT_4) and TSH determinations.

IGF-1 was measured by IRMA (Giuliana Cremascoli Chemical, Segrate, Italy). Interassay coefficient of variation (CV) was <12%; intraassay CV was <8%.

Procollagen type I carboxyterminal propeptide (PICP) concentrations were determined by RIA (Procollagen PICP ^{125}I, Orion Corp., Turku, Finland) as described by Melkko [1990]. Sensitivity of the assay was 1.2 μg/liter; intraassay precision ranged from 2.1 to 3.2%; interassay precision ranged from 4.0 to 6.6%. All parameters were measured 6 months before and after 6 and 12 months of treatment.

Roentgenograms of the lower limbs and of the left wrist were also performed at the same dates. The former were taken according to specific technical criteria to get precise measurements of the length of the femur, in order to have a reproducible index of the effect of r-hGH on the linear skeletal growth in achondroplasia. The left wrist roentgenograms were read by the Tanner–Whitehouse method for the determination of bone age [Tanner et al., 1975].

MRI at the cervicomedullary junction and CT scan of the base of the skull allowed us to detect possible variations of the diameter of the foramen magnum compared to the baseline determination. We used the foramen magnum growth curves in achondroplasia [Hecht et al., 1989] to compare the sagittal and transverse dimensions obtained from the CT scan images of our patients.

RESULTS

During the first semester of treatment growth velocity increased in four patients compared to baseline (range: 1.3–4.1 cm/year). Only one patient did not show any changes in growth velocity during the first semester, but she showed an increase of 5.8 cm/year, compared to baseline, during the second semester. The growth velocity of the other patients did not change during the second semester. The growth velocity increase during the year of treatment ranged from 1.1 to 2.6 cm/year in three patients, while in the others no variations were detected (Table I).

As shown in Table II, neither variations of the sitting/standing height ratio nor remarkable changes of bone age were observed during the treatment.

Growth velocity of the femurs (measured on roentgenograms) increased in all patients but it was not related to the response of the growth velocity to the treatment (Table II).

In 3 out of 6 patients there was an increase of PICP serum levels after 6 months of therapy (Fig. 1). This was particularly remarkable in the patient with the greatest increase of height velocity at the same date (patient 1). PICP levels could not be determined in patient 2.

In Figure 2 we show the trend of IGF-1 levels before and during the therapeutical trial: the most significant increase was observed in a patient with a poor response to the treatment (patient 6). IGF-1 could not be assessed in patient 2.

Thyroid function and oral glucose tolerance test at the beginning and at the end of the therapy were in the normal range in all the patients.

The sagittal and transverse dimensions of the foramen magnum of all the subjects were within the range of the values for the achondroplastic population. No narrowing of the foramen magnum was detected at the neuroradiological examination at the end of the trial. Moreover no signs of acromegaly were present in these children (shoe-size and total hand length did not vary remarkably during therapy).

DISCUSSION

Achondroplasia is the most common skeletal dysplasia in man. It is easily recognizable at birth and there

TABLE I. Auxological Data Before and During GH Treatment

			Growth velocity (cm/year)			
Patient	Age	Sex	Before	1st sem	2nd sem	Total
1	5 y	F	5.1	9.2	5.0	7.1
2	3 y 6 m	F	6.3	7.8	4.8	7.4
3	7 y	F	4.0	4.2	9.8	6.6
4	4 y 7 m	M	4.2	5.8	3.2	4.8
5	8 y 5 m	F	4.1	5.4	2.2	3.8
6	2 y 11 m	F	6.6	4.6	6.0	5.3

TABLE II. Sitting/Standing Height Bone Age/Height Age Ratios and Femur Growth Velocity Before and During GH Treatment

	Sitting/standing height ratio		Bone age/height age ratio		Femur growth velocity (mm/year)	
Patient	Pretreatment	In treatment	Pretreatment	In treatment	Pretreatment	In treatment
1	0.69	0.68	1.0	0.9	15	35
2	0.68	0.68	1.3	1.14	—	15
3	0.70	0.69	1.01	1.12	14.4	17
4	0.70	0.68	0.65	0.9	11.2	16.6
5	0.69	0.68	0.8	0.8	5.1	8.5
6	0.72	0.70	0.7	0.8	17	25

is usually little confusion about the diagnosis. The adult stature of these patients is seriously impaired with serious problems in everyday life. Although the cause of the defect in cartilage growth and endochondral ossification is still unknown, linkage studies recently reported by three different groups mapped the disease to chromosome 4p16.3 [Francomano et al., 1994; Le Merrer et al., 1994; Velinov et al., 1994]. Moreover in homozygous and heterozygous achondroplastic patients a recurrent point mutation has been found in the transmembrane domain of the fibroblast growth factor receptor 3 gene (FGFR3 gene), mapping in the same region of the chromosome 4 [Rousseau et al., 1994; Shiang et al., 1994; Stoilov et al., 1995; Bellus et al., 1995]. Interestingly, this mutation was almost always the same and resulted in the substitution of an arginine for a glycine at position 380 of the protein. Additional evidence that reported mutation is significant in achondroplasia was provided by the cosegregation of the bases substitution with the disease in familial forms and its de novo occurrence in sporadic cases [Rousseau et al., 1994; Shiang et al., 1994; Stoilov et al., 1995; Bellus et al., 1995].

The most common therapeutical approach to this kind of chondrodysplasia is still limb lengthening [Aldegheri et al., 1988; Villarubias et al., 1989] although treatment with r-hGH has been recently proposed with controversial results. Yamate et al. [1993] have reported a significant increase of growth velocity in prepubertal and pubertal achondroplastic children after 6 months or 1 year of GH therapy at the standard doses. A 6 month therapeutical trial carried out in 6 patients with achondroplasia showed a variable response depending on pretreatment growth velocity [Horton et al., 1992]: the lower the growth rate before therapy the greater the increment observed. A reason for the variation in response to GH therapy observed among the treated cases could be the different ages and pubertal stages of the enrolled children.

In our study we chose to treat only prepubertal achondroplastic children in order to obtain homogeneous results as much as possible. We used an r-GH dose similar to that reported by other authors [Okabe et al., 1991; Horton et al., 1992; Nishi et al., 1993] in order to minimize the possible side effects of the treatment and to contain its financial cost.

Our data suggest that recombinant hGH in doses used to treat GH-deficient patients modestly increases short-term growth velocity only in some patients with achondroplasia. Growth velocity increased, on the av-

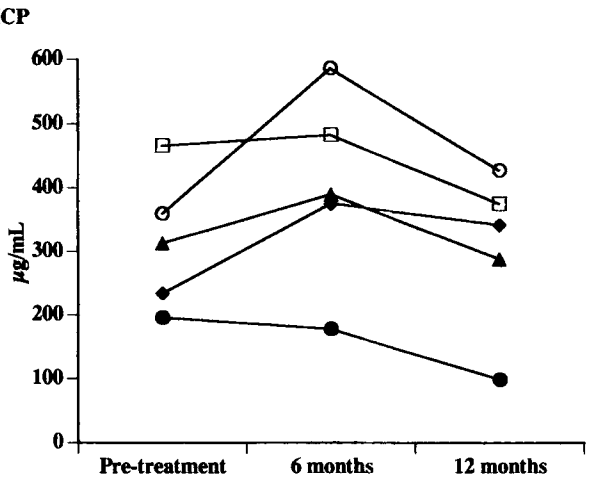

Fig. 1. PICP serum concentrations of achondroplastic children before and during the treatment with growth hormone. Patient 1 (○); patient 3 (●); patient 4 (▲); patient 5 (♦); patient 6 (□).

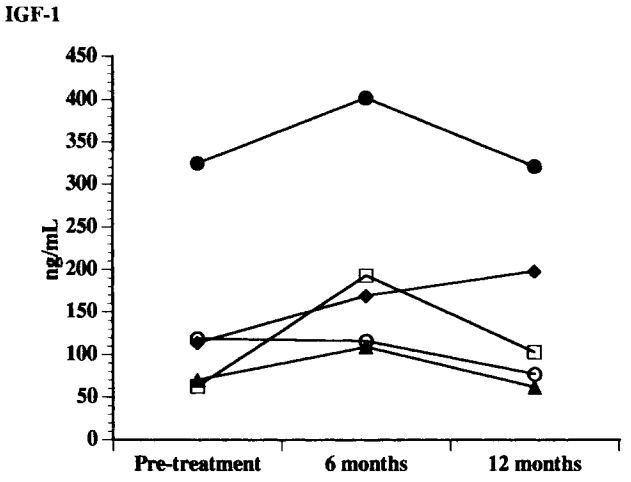

Fig. 2. IGF-1 serum concentrations of achondroplastic children before and during the treatment with growth hormone. Patient 1 (○); patient 3 (●); patient 4 (▲); patient 5 (♦); patient 6 (□).

erage, of 2.1 cm/year in the first semester of therapy in four patients. The variation of the response did not seem to be correlated to pretreatment growth velocity. As mentioned above, other authors [Horton et al., 1992] have previously reported a better response to GH after a 6-month trial in patients with low growth rate before treatment; in these patients no GH provocative test was done. We obtained the best result in the girl who had the lowest peak of GH (albeit in the normal range) at the provocative test with clonidine. Unexpectedly, IGF-1 levels were not related to the growth velocity. Similarly we did not find any relationship between PICP levels and growth velocity. Owing to either the limited number of patients or to the widespread range of the results it is not possible to draw any conclusions concerning the role of these parameters in monitoring the efficacy of such therapy. Larger studies are needed to clarify the role of the radiological evaluation of femur growth velocity as a parameter of linear skeletal growth in achondroplastic children.

In all patients but one the growth velocity in the second trimester decreased compared to baseline, suggesting a possible reduced efficacy of the treatment with time. A similar trend was reported in hypochondroplastic children treated with GH for up to 3 years [Bridges et al., 1991].

No side effects were observed during the study. In particular there was no evidence of spinal cord compression or narrowing of the foramen magnum. Thus, GH treatment does not seem to affect the growing structure of the cranial base. Moreover, we did not observe any acromegalic-like signs or a worsening disproportion between trunk and lower limbs: the ratio sitting/standing height was almost unchanged after treatment compared to baseline.

In previous studies bone age was not determined because of the difficulty in interpreting the altered roentgenographic findings in achondroplastic children [Horton et al., 1992]. We had to face the same problem and, in order to reduce the error of determination, we used the Tanner–Whitehouse method for bone age. In two children bone age increased more than 1 year during the year of therapy. However, no remarkable changes of the bone age/height age ratio was observed at the end of the trial.

In summary, our study shows that r-hGH can safely increase short-term growth velocity in some prepubertal children with achondroplasia. Larger studies are needed to evaluate the factors affecting the variable responses to the treatment and the efficacy of a long-term therapeutical trial. The latest molecular data may give new insights into the pathogenesis of achondroplasia and its therapeutical aspects. As in Turner syndrome, larger doses of GH could be needed to get more remarkable growth-promoting effects in achondroplastic children.

In conclusion, we believe that therapeutical attempts with r-hGH should be considered in achondroplastic children. The treatment should be continued until a positive effect on growth velocity is recorded. The treatment with r-hGH, followed by surgical lengthening of the limbs during adolescence, may contribute to improve the final height in achondroplastic patients.

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